Clinical Pharmacology Issues with Pediatric Formulations

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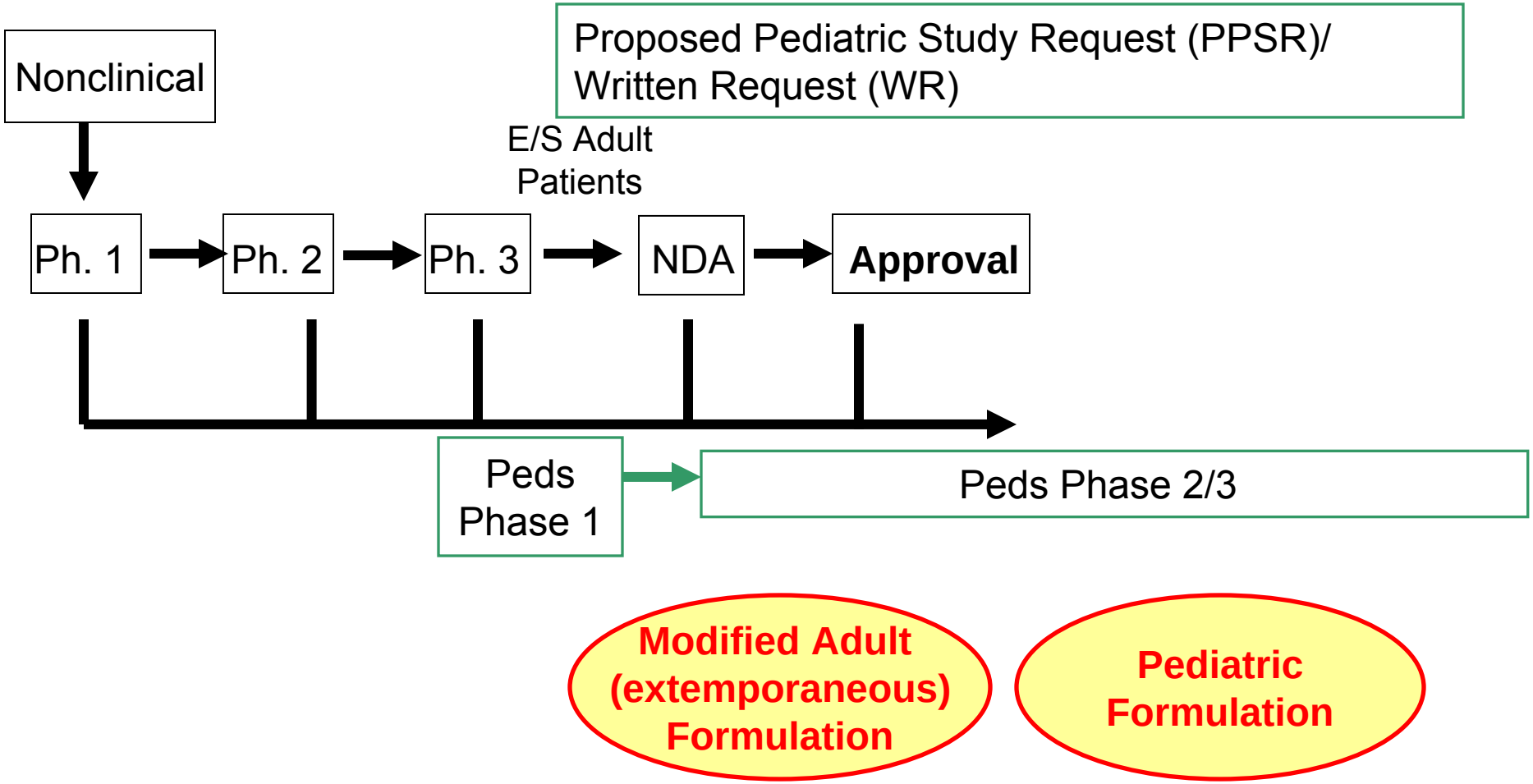
Outline

1. Background: pediatric drug/formulation development paradigm
2. Clinical pharmacology issues
   - What is the bioavailability (BA)?
   - How is it going to be administered?
3. Summary

Typical Drug Development Begins in Adults, Then It Moves to Pediatrics

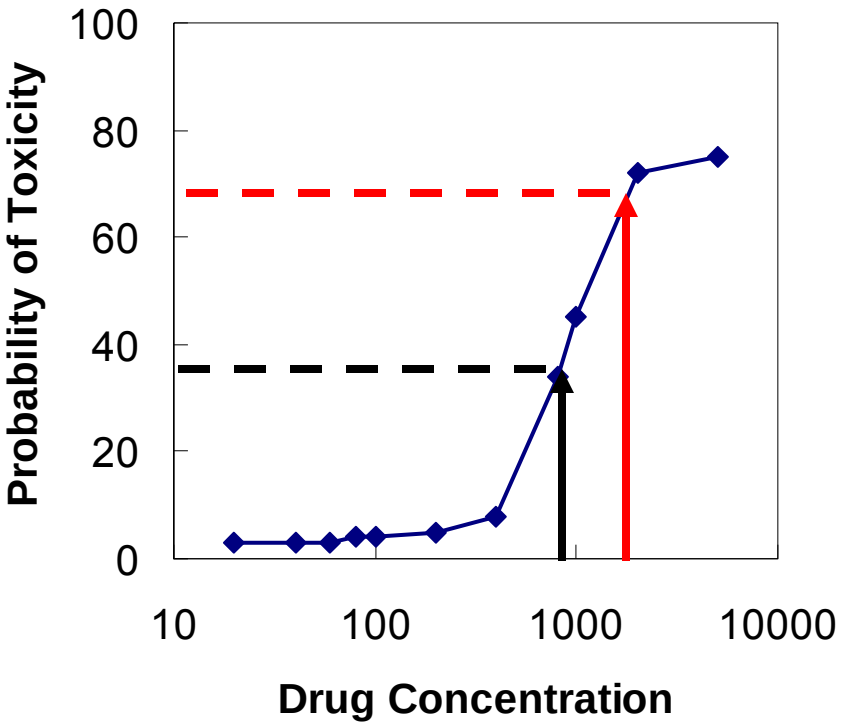


Clin Pharm Issues with Pediatric Formulations

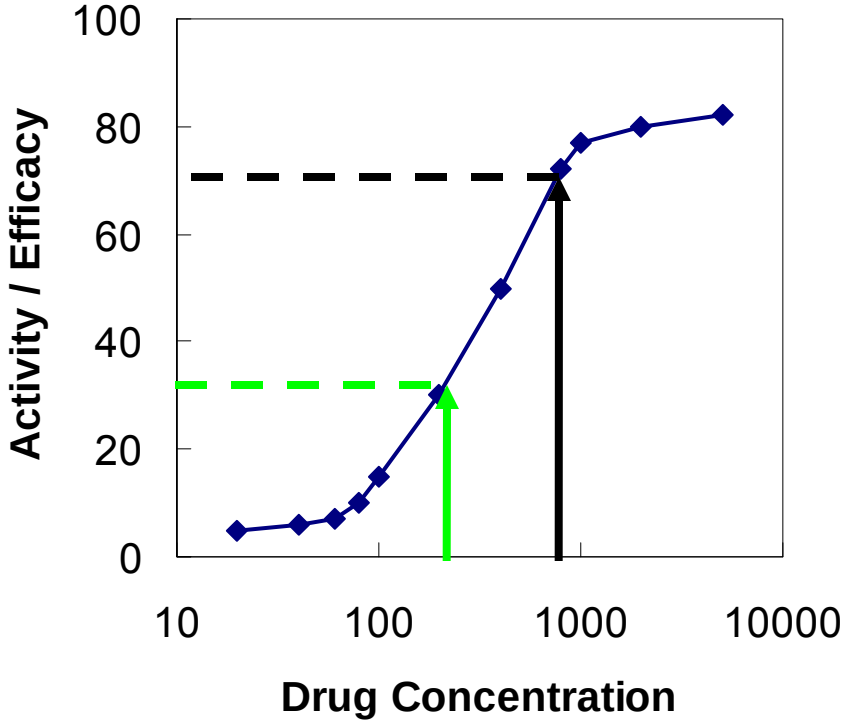
- What is the BA of the new formulation?
  - Pediatric formulation
    - e.g., suspension, syrups, sprinkles, chewable tablets, orally dissolving films
  - Modified adult (extemporaneous) formulation
- How is it going to be administered?
  - Opened capsule or crushed tablet
  - Mixing with food/beverage

Why do we care?

- These factors can increase or decrease drug exposure, leading to toxicity, or ineffectiveness!



Increased toxicity, as indicated by the red line



Reduced effectiveness, as indicated by the green line

BA of the Pediatric Formulations

" Bioavailability of any formulation used in the (pediatric) studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults."

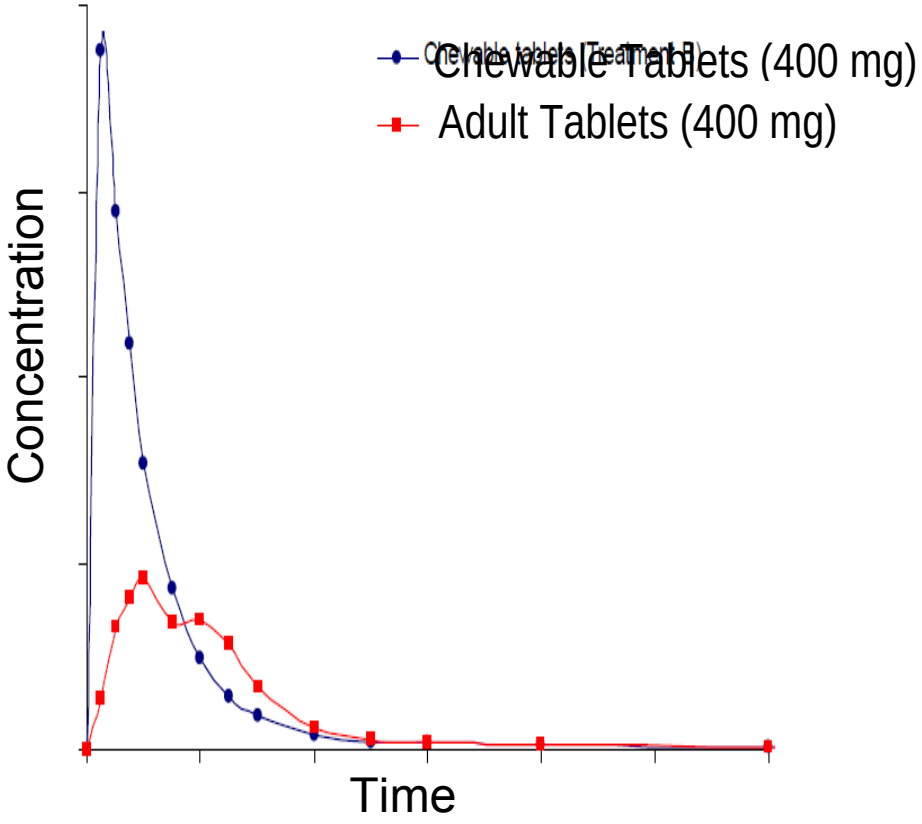
-Pediatric Written Request Template

http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

Example 1
ISENTRESS® (raltegravir)

- Dosage forms and strengths:
  - Film-Coated Tablets: 400 mg
  - Chewable Tablets: 100 mg scored and 25 mg

- The film-coated tablets cannot be substituted with the chewable tablets on a mg:mg basis.
  - In a relative BA study in healthy adults, the chewable tablet has higher BA compared to the film-coated tablet.
  - Both formulations were tested in a Phase I/II pediatric trial to evaluate PK, safety, tolerability, and efficacy.



Example 1
ISENTRESS® (raltegravir)

- Dose recommendation is based on patients' age and body weight, as well as the formulation used.
  - **12 years of age and older:** One 400 mg film-coated tablet, twice daily.
  - **6 to < 12 years of age:**
    - If ≥ 25 kg : One 400 mg film-coated tablet, twice daily **OR** Chewable tablets: weight based to maximum dose 300 mg twice daily
    - If < 25 kg : Chewable tablets: weight based to maximum dose 300 mg twice daily.
  - **2 to < 6 years of age:** If ≥ 10 kg: Chewable tablets: weight based to maximum dose 300 mg twice daily.

BA information of the pediatric formulation is important for dosing decisions.

Example 2: GLEEVEC® (imatinib mesylate)

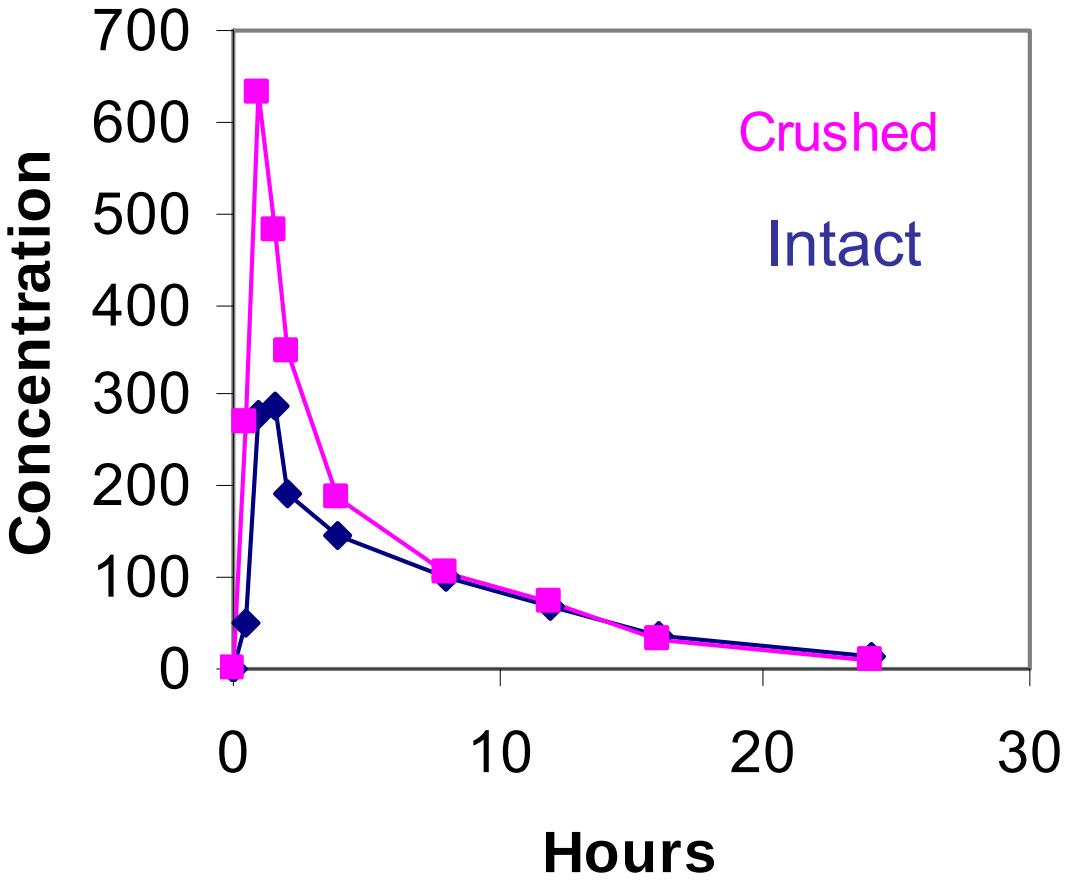
- Dosage forms and strengths:
  - Tablets (scored): 100 mg and 400 mg
- No specific pediatric formulation
- Extemporaneous formulation:
  - The tablets dispersed in water or apple juice to make a suspension, and administered immediately
  - In a BA study in adults, the bioequivalence (BE) between a capsule formulation (which is BE to the tablets as demonstrated in another study) and an oral solution has been established

BA information can determine whether an extemporaneous formulation can be administered in children.

How is Drug Administered?

- Opened capsule or crushed tablet
- Mixing with food/beverage
- Other factors
  E.g. feeding tubes

Crushed Tablets/Opened Capsules: Why is this a Problem?



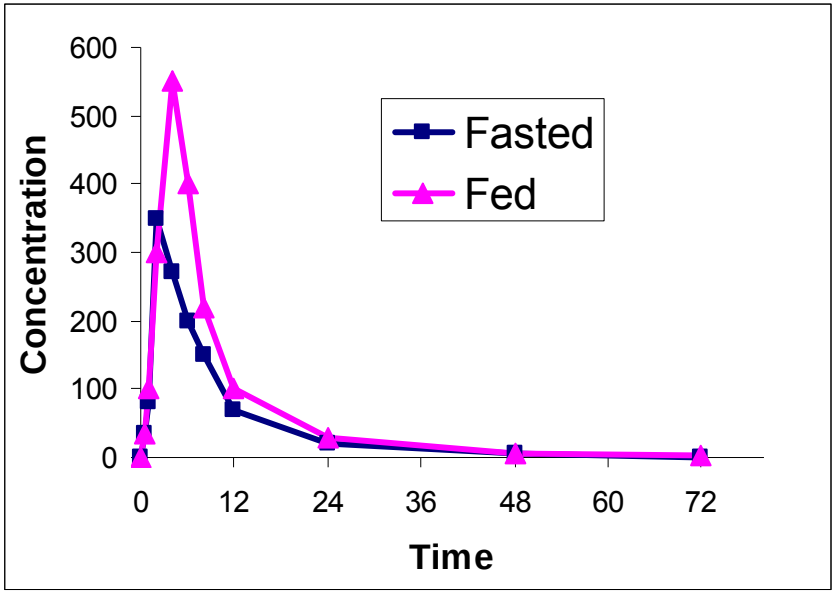
- Dose-dumping
  → Increased Cmax
  →Increased Toxicity

- Area under the curve (AUC) can also increase or decrease
  → toxicity or ineffectiveness

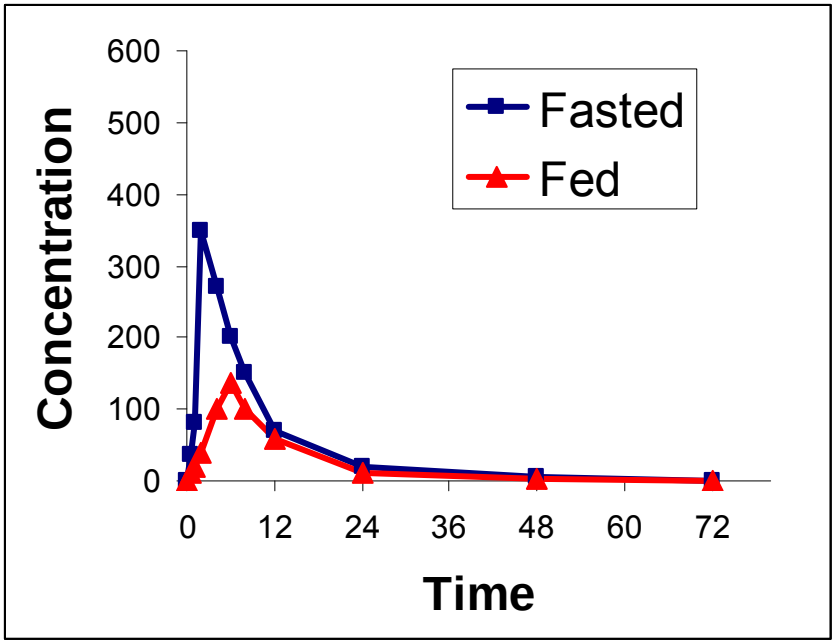
- Product quality issues:
  Stability, etc

Administration with Food/Beverage: Why is this a Problem?

They can impact the rate and/or extent of absorption of a drug.



Increase Cmax and/or AUC, leading to toxicity!



Decrease Cmax and/or AUC, leading to ineffectiveness!

Example 3 (Drug X)

- PPSR submitted after the drug developed in adults
- Adult formulation: Capsule
  - Food can increase the AUC and Cmax
- No pediatric formulation
- In the proposed pediatric trial, the capsule will be opened and administered with a range of food/drink
- Significant concern about dose dumping and food effect
  - In adults, increased AUC and Cmax are associated with toxicity
- FDA requested a BA study to be conducted before the initiation of the pediatric trial

The impact of drug administration method should be evaluated before the pediatric trial initiation.

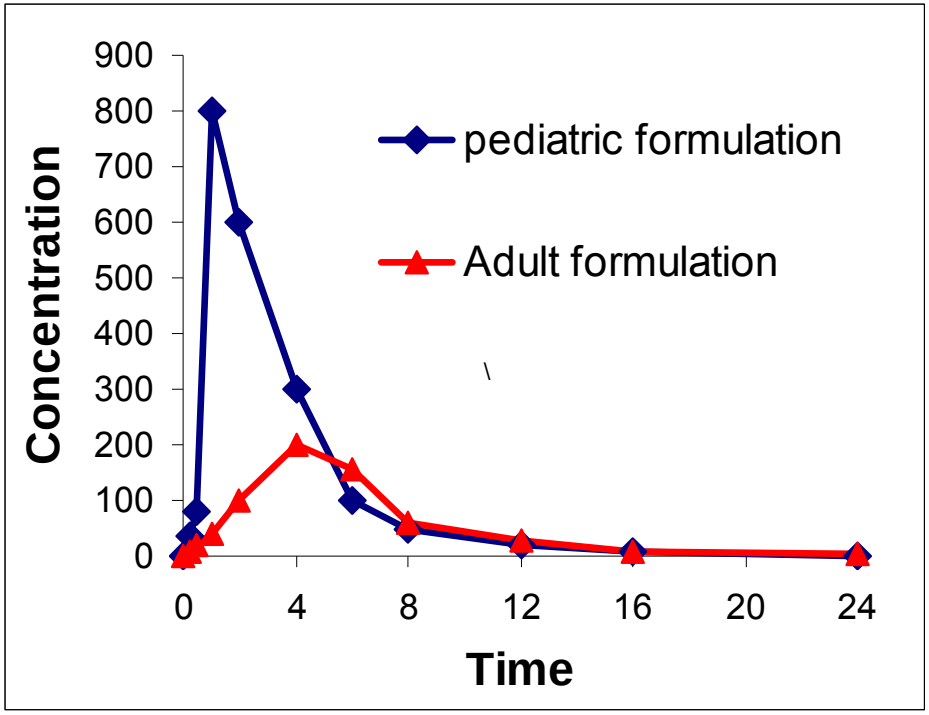
How Should We Address the Issues?

…by studying their impact on Pharmacokinetics (PK):

- BA studies
- Food effect studies

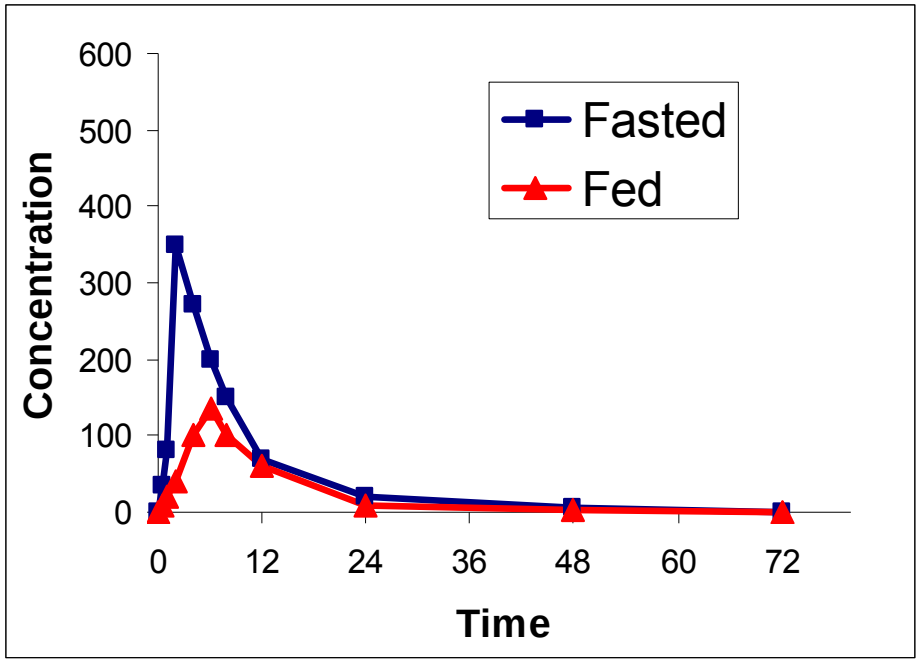
BA Studies

$$\textit{Relative BA} = AUC_{peds\_formulation} / AUC_{adult\_formulation}$$



- Can be conducted in adults
- Comparing the PK of the different formulations
- Allow us to scale the dose for the pediatric formulation

Food Effect Studies



- Can be conducted in adults
- Comparing the PK under fasted and fed condition
- Considerations should be given to the typical kids food/drink
- Allow us to determine how to administer the drug in children

What Paradigm Do We Propose?

If change in formulation or administration methods, need to consider **their impact on BA again**

Relative BA and food effect study in adults → **Peds Phase 1** → **Peds phase 2/3**

Collect PK from pediatric patients to make sure the appropriate exposure

Summary

- Clinical pharmacology issues
  - What is the BA of the new formulation?
  - How is it going to be administered?

- They can increase or decrease drug exposure, leading to toxicity or ineffectiveness!

- Need to be address early
  - Scale dose better/avoid toxicity and ineffectiveness
  - Make the pediatric trial safer and more effective

Thanks

- Brian Booth
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